Is prophylactic central neck dissection justified in patients with cN0 differentiated thyroid carcinoma?

An overview of the most recent literature and latest guidelines

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Is prophylactic central neck dissection justified in patients with cN0 differentiated thyroid carcinoma? An overview of the most recent literature and latest guidelines

To date, in patients with differentiated thyroid cancer, central neck dissection is recommended in the presence of central compartment lymph node metastases. Differently, the efficacy of prophylactic central neck dissection in case of clinically node-negative differentiated thyroid carcinoma remains still uncertain. There are many arguments in favor and many against the execution of this surgical procedure.
The most recent literature and latest guidelines have been reviewed and illustrated, paying particular attention to currently hottest and most discussed points.
Prophylactic central neck dissection is associated with higher rates of postoperative complications, such as recurrent laryngeal nerve injury and hypoparathyroidism, with unclear oncological benefits. Thus, in the absence of lymph node involvement, this procedure should be avoided, reserving it for high-risk patients with advanced primary tumors. Moreover, to avoid serious complications, prophylactic central neck dissection should be performed by high-volume surgeons.

KEY WORDS: Clinically node-negative differentiated thyroid cancer, Differentiated thyroid carcinoma, Prophylactic central neck dissection

Background

Differentiated thyroid cancer (DTC) is the most common malignancy of the thyroid gland and the most common endocrine malignant neoplasm [1]. The incidence of thyroid cancer has increased drastically in the last decades [2,3]. It is the most rapidly increasing carcinoma (>5% per year in both men and women), with an estimate of 64.300 new cases diagnosed in the United States in 2016 [4].

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Papillary thyroid cancer (PTC) is the most common histopathological subtype of DTC, accounting for about 80-85% of thyroid malignancy [2,5-8].
The prognosis for DTC patients after treatment is excellent, with 10-year survival rates exceeding 90% and 15-year survival rates > 87% [1,4,5,9]. However, unfortunately, even in clinically node-negative (cN0) DTC, cervical lymph node metastases (LNM) occur in up to 20-80% of patients. Micrometastases are instead reported in 40-90% of cases [15,16].
Cervical LNM mostly involve the central compartment of the neck, comprising the pretracheal, prelaryngeal (Delphian) and paratracheal nodal basins [1,3,4,8,10-14].
The presence of cervical LNM confers an increased risk of loco-regional recurrence (LRR), however, it has tra-

ditionally been considered to have no impact on overall survival [10,17-19]. Recent studies have instead indicated that the presence of cervical LNM not only increases the risk of LRR but also has an adverse effect on survival, especially in older patients (age > 45 years) [5,6,10,20-23]. In a recent large population-based study, cervical LNM were associated with an increased risk of mortality [6,9]. However, the high LRR rate (equal to 15-30%) represents the main problem in clinically node-negative DTC patients, seriously affecting their postoperative quality of life [1,5,6,24].

Prophylactic central neck dissection (PCND) may decrease LRR, thus reducing the need for reoperation, and improve disease-specific survival. Moreover, the difficulty in diagnosing cervical LNM accurately by preoperative ultrasound (US) or intraoperative inspection, the detection of subclinical cervical LNM in up to 60% of patients, the lack of accurate histopathological staging without lymph node analysis, the better thyroglobulin (Tg) surveillance, the failure of 131I ablation in approximately 30% of cases and the improved ability to justify radioactive iodine (RAI) treatment are considered factors in favor of PCND [1,13,15-17]. However, its effectiveness in patients with clinically node-negative DTC remains still controversial [1,2,4,16,21,22,25-27-28].

Pre and Intraoperative Evaluation of Lymph Nodes of the Central Compartment

Clinical examination, in some cases, can detect the presence of LNM in the lateral compartment, while it is not useful for the evaluation of the lymph nodes of the central compartment [23,29].

Preoperative US and contrast-enhanced computed tomography (CT) are not sensitive in detecting LNM in the central compartment because metastatic lymph nodes are usually small and, moreover, are obscured by the overlying thyroid gland [8].

Despite the high diagnostic accuracy of US in detecting lateral cervical LNM (with a sensitivity of 94%), preoperative US diagnosis of LNM of the central compartment is technically challenging and often unreliable due to the proximity to the air-filled trachea and thyroid gland [14]. Moreover, being US highly user-dependent, it should be performed by an experienced surgeon or radiologist [12]. Among sonographic features of lymph nodes which are suspicious for metastatic disease, cystic areas, microcalcifications, peripheral vascularity and short axis (> 5 mm) are specific, while the loss of fatty hilum and peripheral vascularity are sensitive [30].

The sensitivity of CT scan is low, ranging from 39% to 66%, and its accuracy is of 66% [12,31]. The combined use of US and CT shows a sensitivity of 48-54% and an accuracy of 66-69% [12]. However, this accuracy remains unsatisfactory for decision-making [12].

Fine-needle aspiration cytology (FNAC) associated with Tg measurement is the more accurate diagnostic method for cervical LNM from thyroid cancer (when they are visible preoperatively) [32].

Intraoperative detection of metastatic lymph nodes by the surgeon has been demonstrated to be unreliable [12]. Moreover, in patients with DTC and concomitant autoimmune thyroiditis, the presence of slightly enlarged or firm lymph nodes is difficult to correlate with the presence of lymph node metastases [12,20].

Sentinel lymph node biopsy shows an inconsistent pattern of nodal spread, and, therefore, does not seem to be readily transferable to thyroid surgery [20]. Similarly, the role of frozen section evaluation of sampled lymph nodes to identify metastatic disease requiring central neck dissection (CND) remains still unclear [20].

Current Guidelines and Consensus Statements

The 2009 American Thyroid Association (ATA) guidelines recommend therapeutic CND in case of clinically positive LNM of the central compartment and PCND in patients with T3 or T4 primary cancers (without clinical evidence of LNM of the central compartment) or with known lateral cervical LNM. These general recommendations remained unvaried in the 2015 update, with the addition that PCND can be executed if the information obtained following its execution can guide further steps of treatment [22].

A consensus of the European Society of Endocrine Surgeons (ESES) recommends that PCND should be risk-stratified. Patients with large tumors, age > 45 or < 15 years, multifocal or bilateral tumors or known involvement of lateral cervical lymph nodes could receive PCND. These guidelines also state that PCND should be performed by experienced endocrine surgeons [33].

The British Thyroid Association (BTA), in its 2014 guidelines, considering the high incidence of postoperative complications, recommended not to perform routine PCND. This association stated that decision-making should be personalized [34].

In line with ATA guidelines, the Italian Association of Endocrine Surgery Units (U.E.C. CLUB), in 2016, and subsequently, in 2018, six Italian societies (the Medical Endocrinology Association, the Italian Thyroid Association, the Italian Association of Nuclear Medicine and Molecular Imaging, the Italian Society of Endocrinology, the Italian Society of Anatomic Pathology and Diagnostic Cytology and the Italian Society of Unified Endocrine Surgery) recommended not to perform PCND routinely [22,35,36].

The National Comprehensive Cancer Network (NCCN) expert panel assigned to PCND a category 2B recommendation, stating that it could be considered for cases with T3 or T4 carcinomas, taking into account the increased risk of postoperative complications [12].

On the contrary, the Japanese Association of Endocrine

Surgeons (JAES) and the Japanese Society of Thyroid Surgeons (JSTS) recommend routine PCND, on the basis of the increased risk of complications in case of surgery for lymph node recurrence [37].

Surgical Anatomy of the Central Compartment and Definition of Central Neck Dissection

The central compartment is composed of level VI and level VII [12]. Knowing its anatomic boundaries is very important. This region is bounded anteriorly by the superficial layer of the deep cervical fascia, superiorly by the hyoid bone, laterally by the carotid arteries, inferiorly by the innominate artery and posteriorly by the prevertebral layer of the deep cervical fascia.
This compartment includes pretracheal, prelaryngeal (Delphian), paratracheal and paralaryngeal lymph nodes [12,20].
Level VII, in particular, is composed of the superior anterior mediastinal lymph nodes, located above the innominate (brachiocefalic) artery and below the level of the upper border of the sternal manubrium [12,20].
The majority of the lymph nodes within the central compartment are situated inferior to the larynx, while lymph nodes of this region most commonly involved in DTC are prelaryngeal (Delphian), paratracheal and pretracheal lymph nodes [12,20,31].
Superior pole carcinomas can metastasize to parapharyngeal lymph nodes deep to the omohyoid and sternohyoid muscles along the course of superior thyroid vasculature and to the retropharyngeal space [12].
CND is defined as the excision of level VI and VII lymph nodes (on the basis of the recognized anatomic continuity between the superior mediastinum and neck) [15].

Complications of Central Neck Dissection

Increased rates of postoperative complications have been observed in patients undergoing CND, especially when performed by low-volume surgeons [1,12,15]. The complications associated with CND include transient or permanent hypoparathyroidism, in case of devascularization or inadvertent removal of parathyroid glands, and recurrent laryngeal nerve (RLN) injury, with resulting dysphonia [22,26,38].
The rate of transient RLN lesion ranges from 0% to 7.3%, while that of permanent RLN injury ranges from 0% to 5.9% [31,39,40]. Intraoperative neuromonitoring can be helpful to identify a loss of signal on the first side that could suggest performing a two-stage thyroidectomy, especially in patients with non-aggressive carcinomas [31,41].
The rate of transient hypoparathyroidism, in the literature, is extremely variable, ranging from 8.7% to 86%, while the rate of permanent hypoparathyroidism ranges from 0% to 16.2% [31,39,40]. Transient hypoparathyroidism after CND occurs in 14-40% of patients in high-volume centers [20,24]. Recent studies demonstrated that the overall prevalence of temporary hypocalcemia after TT with CND is significantly higher than after TT alone [12]. The risk of postoperative hypocalcemia is between 2.0 and 2.7 times higher when CND is executed [10]. It is important to emphasize that in 87-95% of cases, transient hypoparathyroidism recovers within 6 months after surgery [1]. The higher rate of postoperative hypoparathyroidism in case of CND is likely secondary to the close relationship of level VI lymph nodes with inferior parathyroid glands. Thus, for this reason, these glands are often removed or devascularized during CND [18].
Moreover, inexperienced surgeons are associated with greater rates of postoperative complications [19].
To decrease the risk of complications related to CND, ipsilateral CND, instead of bilateral CND, has emerged as an alternative approach [1,24,39,42].

Complications of Reoperative Central Neck Dissection

Reoperative central neck dissection for recurrent disease is a challenging procedure. Specific data regarding its morbidity is lacking, mainly due to the limited number of patients requiring this kind of operation [31,43].
Indications for revision surgery in the central compartment include DTC recurrence as central compartment lymph node metastases and inadequate primary surgery [31].
Reoperative CND is difficult because of the distorted anatomy and abundant scar tissue, which lead to a higher risk of parathyroid glands and RLN injury. RLN can be in an anomalous location after thyroidectomy and, in addition, RLN and parathyroid glands can be encased within fibrotic tissue, making them difficult to identify and preserve [31].
Recurrent disease is usually detected during follow-up by measuring serum Tg levels and by means of radiological examinations (US, RAI scan or PET/CT), and subsequently confirmed through FNAC and contrast-enhanced CT or MRI [31].
Several studies reported a higher incidence of permanent RLN injury in case of reoperative CND compared with primary surgery, with rates ranging from 1% to 12% [31,43]. Moreover, a higher incidence of transient and permanent hypoparathyroidism after revision surgery has been described, ranging from 0.3% to 15% and from 0% to 4.9%, respectively [23,31,43].
Due to the high complexity of reoperative central neck dissection and knowing the correlation between surgeon experience and outcomes, surgery for recurrent disease in the central compartment should be performed by experienced thyroid surgeons.

Risk Factors for Central Compartment Lymph Node Metastases

Factors increasing the risk of central compartment LNM include age, gender, familiarity, tumor size, aggressive variants of DTC, extrathyroidal extension, multifocality and bilaterality, BRAF V600E mutation and lymphovascular invasion [1,5,10-12,15,16,18,19,21,26,44].

Age is one of the most important prognostic factors of DTC [3,8]. In patients older than 45 years and in those younger than 15 years DTC is more often associated with worse prognosis and increased recurrence rates [16].

Male gender is another significant risk factor of central compartment LNM [1,4,19,44].

The tumor size is a very important prognostic factor. Large tumors are more prone to be aggressive [3,9,16]. The tumor dimension has been repeatedly confirmed as an independent predictor for clinical outcomes. It is well known that cervical LNM increase with malignancy size: larger tumors (> 1 cm) are associated with an increased risk of central compartment LNM [16,19]. The tumor size (> 5 mm) is also a significant predictive factor of central compartment LNM in microcarcinomas [8,16,44]. Multifocality and bilaterality have been associated with increased rates of central compartment LNM in PTC [8,9,26].

Lymphovascular invasion and extrathyroidal extension have been found to be associated with an increased risk of central compartment LNM in DTC [8,44]. Capsular invasion, in particular, is associated with LNM in this region [8].

The BRAF V600E mutation has been associated with aggressiveness of DTC (onset of cervical LNM) and also with disease-specific mortality, especially when associated with other aggressive features [16,20]. However, BRAF V600E mutation analysis offers a very low positive predictive value (28%) for disease recurrence [20].

It is important to note that cancers in the upper pole of the thyroid gland are associated with higher rates of lateral cervical LNM, while those in the lower pole have an increased risk of central compartment LNM [8].

Moreover, cases of skip metastases to lateral cervical lymph nodes (no LNM in the central compartment) occur in up to 18% of cases. They occur more commonly in superior pole neoplasms [16,20].

A very important limitation of some of these risk factors is that they are based on the histopathological examination, which is available after surgery, when the decision about the execution of CND has already been taken [12].

Discussion

PCND can reduce LRR and improve disease-free survival. However, it increases the risk of hypoparathyroidism and RLN lesions [16].

Several prospective studies have demonstrated that this approach is able to decrease serum Tg levels and, as a consequence, is associated with a greater rate of postoperative athyroglobulinemia [42].

PCND can improve staging accuracy and patient selection for RAI treatment. Moreover, decreasing the risk of LRR, PCND reduces the need for reoperation [18,23,42,45].

It is important to emphasize that PCND has increased the rate of recourse to adjuvant RAI therapy [1]. This surgical procedure, in fact, leads to an upgrade of TNM staging in 30% of cN0 DTC patients, making RAI and long-term TSH suppressive treatment necessary [1]. RAI therapy is associated with potential morbidity, including salivary gland swelling, recurrent sialadenitis and salivary gland dysfunction (which can cause chronic dry of mouth and throat, increased dental caries and loss of teeth). Moreover, it can cause ageusia, leukopenia, lacrimal gland dysfunction and nasolacrimal outflow obstruction, nausea, vomiting, ovarian dysfunction and menstrual irregularities in women, decreased sperm count in men, dysphagia, pulmonary fibrosis and second primary malignant neoplasms [11,16,46]. RAI treatment is also associated with increased financial costs [46].

Higher morbidity rates, uncertain significance of lymph node involvement, absence of proven benefits on survival, the upgrade of TNM staging and the RAI therapy overuse (with its undesirable side effects) were invoked against PCND [16,28].

To reduce morbidity PCND should be performed by experienced endocrine surgeons [16].

The American Thyroid Association assessed feasibility of performing a randomized controlled trial to evaluate the benefit of PCND. This committee estimated that a clinical trial with enrollment of 5840 patients, spanning 7 years and with a total study cost of approximately $20 million ($3425 per enrolled study subject) would be necessary. It was therefore concluded that such a randomized controlled trial is not readily feasible [12].

Conclusions

To date, there is still no consensus on the role of PCND in case of clinically node-negative DTC. PCND is associated with higher rates of complications, such as RLN injury and hypoparathyroidism, without clear oncological benefits. Thus, in the absence of lymph node involvement, this procedure should be avoided, reserving it for high-risk patients with advanced primary tumors. Moreover, to avoid serious complications, PCND should be performed by high-volume surgeons.

Riassunto

Attualmente, nei pazienti con carcinoma tiroideo differenziato, la linfectomia del comparto centrale del col-

lo è raccomandata in presenza di metastasi linfonodali in tale sede. L'efficacia della linfectomia profilattica del comparto centrale nel carcinoma tiroideo differenziato con linfonodi clinicamente negativi rimane invece ancora controversa.

Esistono diversi argomenti a favore e diversi contro l'esecuzione di questa procedura chirurgica. Sono state revisionate ed illustrate la letteratura più recente e le ultime linee guida, prestando particolare attenzione ai punti più caldi e discussi.

La linfectomia profilattica del comparto centrale è associata a tassi più elevati di complicanze postoperatorie, come lesioni del nervo laringeo ricorrente ed ipoparatiroidismo, con benefici oncologici poco chiari.

Pertanto, in assenza di coinvolgimento linfonodale, tale procedura dovrebbe essere evitata, riservandola a pazienti ad alto rischio con tumori primari avanzati. Inoltre, per evitare gravi complicanze postoperatorie, questa la linfectomia profilattica del comparto centrale dovrebbe essere eseguita da chirurghi ad alto volume.

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